"COMPARISON STUDY OF TOPICAL RETINOIDS ADAPALENE Vs TAZAROTENE IN THE TREATMENT OF ACNE VULGARIS"

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CERTIFICATE

This is to certify that this dissertation titled **"COMPARISON STUDY OF TOPICAL RETINOIDS ADAPALENE Vs TAZAROTENE IN THE TREATMENT OF ACNE VULGARIS"**is a bonafide work done by Dr.R.AMUDHA, Post Graduate Student of the Department of Dermatology, Venereology and Leprosy, Madras Medical College, Chennai – 600 003, during the academic year 2006-2009. This work has not previously formed the basis for the award of any degree.

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CONTENTS

INTRODUCTION

Acne Vulgaris is an extremely common disease with increased prevalence among adolescents. Although acne is not a life-threatening condition, it can cause substantial morbidity. Acne and resulting scarring can have a psychological impact including lowered self image and self-esteem, social impairment and anger. Even those with minimal acne experience psychological effects and for those people, the psychosocial burden may be the most significant problem with this disease. It has been shown that even clinically mild to moderate acne can be associated with higher rates of depression and suicidal thoughts among adolescents than other chronic and disfiguring skin diseases. In summary, acne is an important condition and appropriate intervention is essential to prevent complications such as acne scarring, psychological impacts and secondary impaired social function.[1]

In the last 25 years, numerous topical and systemic drugs have been developed for the treatment of acne vulgaris.

The primary lesions of acne are the microcomedones, which are not visible to the naked eye but require special attention with regard to the development of therapeutic strategies. They represent the central

precursor lesions that evolve into either non inflammatory comedones or inflammatory macules, papules and pustules.

Retinoids are derived from Vitamin A. They were first observed to be extremely effective in curing acne since 1962.[2]

Retinoids influence the proliferation and differentiation of cells and therefore reverse the abnormal desquamation by affecting the follicular epithelial turnover. This leads to an expulsion of mature comedones and suppression of microcomedone formation. The change of the microclimate in the pilosebaceous follicle by prevention of hypercornification promotes an inhospitable aerobic environment for P.acnes and is likely to enhance the penetration of other topical drugs. Various in Vitro and in Vivo studies also demonstrated direct antinflammatory activity of topical retinoids. [2,3]

Furthremore, retinoids modulate the expression of the transcription factors, such as AP-1, that regulate genetic expression of growth factors and degradative enzymes involved in inflammatory responses Retinoids are also involved in the induction of apoptosis by a variety of mechanisms either associated with or independent of binding of retinoid receptors.

The results support and give additional theoretical background to explain the significant reduction of inflammatory lesions that have been observed in well-controlled clinical trials of various formulations of adapalene, tretinoin and tazarotene.

Retinoids inhibit the formation and reduce the number of microcomedones in a dose dependent manner as well as non inflammatory and inflammatory lesions. Therefore most acne patients benefit from the use of retinoid, whether a topical agent as monotherapy, or combination therapy and subsequent maintenance therapy.

Topical retinoids are now used as a first-line treatment for most forms of acne, they are also being used as part of maintenance therapy. In the face of an increasing prevalence of antibiotic resistant strains of P.acnes (i.e. P.acnes do not respond to conventional antibiotics), topical retinoids have the potential to minimize antibiotic use in acne. A systematic review is hence required to determine both the efficacy and the safety of topical retinoids in acne treatment.[2,3]

REVIEW OF LITERATURE

Acne vulgaris is a chronic inflammatory, self-limited disease of pilosebaceous unit, seen primarily in adolescents clinically characterized by formation of comedones, papules, pustules, nodules, or pseudo cysts and in some cases accompanied by scarring.[4] Acne vulgaris is a very common physiological malady of adolescents but it is better regarded as a disease due to its inflammatory component and the disfigurements it produces on the socially and psychologically most important body region.

The term ‘comedone’ was suggested by Hoeflt (1846).[1] Samuel plumbe (1795-1837) recognized these primary acne lesions which in some patient evolve into papules, pustules and nodules. The importance of propionibacterium acnes and sebum in the pathogenesis of acne was emphasized by Thibierge (1900). This condition usually starts in adolescence[5] although (some patients present in the first year of life with neo-natal or infantile acne) and frequently resolves by mid twenties. Some degree of acne affects 95% and 83% of 16 year boys and girls respectively.[6] In about 20%, the disease needs the help of physician. A

peak in the incidence and severity occurs between 14 and 17 years in females, 16 and 19 years in male.

The highest concentration of acne lesions are found in the sebaceous rich anatomic areas of face, shoulders, mid-chest, and upper back. The disease is usually self-limited but cases appearing denovo in the second and third decade are not uncommon.

AETIOLOGY AND PATHOGENESIS

Although the basic cause of acne is unknown, there is considerable information on the various factor concerned in its pathogenesis. Acne is a multifactorial disease, developing in the sebaceous follicles.[5]

FOUR PRINCIPLE PATHOLOGIC EVENTS IN ACNE ARE:

1. Seborrhoea
2. Comedo formation (comedogenesis)
3. Colonization of the duct with propionibacterium acnes
4. Mediation of inflammation.

Seborrhoea

Patients with increased sebum production complain of greasy skin, Sebaceous activity is predominantly dependent on androgenic sex hormones of gonadal or adrenal origin. High level of sebum secretion results from high overall androgen production or increased bioavailability

of free androgen due to deficiency of sex hormone binding globulin (SHBG)[7].

Sebum secretion varies from follicle to follicle and certain follicles may be prone to acne. An enhanced peripheral response to androgen must be considered as a probable factor in many subjects.

The possible role of increased 5 α reduction of testosterone to its more active metabolite 5α Dehydrotestosterone (5α – DHT) is supported by the demonstration of high 5α reductase type I activity in the sebaceous gland. This **end-organ hyperresponsiveness theory** for acne suggest that androgen action on sebaceous gland may be independent of serum hormonal levels.

Sebum in acne patients have significant decrease in the level of linoleic acid. This results in follicular hyperkeratosis and decrease epithelial barrier function.

Sebum consists of a mixture of squalene, wax and sterol esters, cholesterol, polar lipids and triglycerides. As the sebum moves up the duct, bacteria, especially P.acnes, hydrolyse the triglycerides to free fatty acids. Lipids may be involved in ductal hypercornification, or may be essential to the growth (stimulation and inhibition) of bacteria. Sampling of skin-surface lipids has shown that patients with acne tend to have

higher levels of squalene and wax esters, lower levels of fatty acids, and a more frequent occurrence of particular free fatty acids. Linoleic acid is significantly reduced in epidermal and comedonal lipids, and this may relate to ductal hypercornification.

Comedogenesis

Kinetic studies have demonstrated that there is an increase in cellular turnover [11] in comedones and their increased adhesion due to persistence of desmosome leads to retention hyperkeratosis. The stimulus for hypercornification may be androgen mediated or the result from the irritant effect of sebaceous free fattyacids. Androgen mediated hypercornification is due to its receptor present in the outer root sheath of infra infundibular region of follicles.[12] Sebum initiate the infundibular keratinocyte leading to release of interleukin 1 alpha. This induces the follicular hyperkeratosis. [13, 14]

Impaired water barrier function is caused by reduced amounts of ceramides which are responsible for comedone formation, since barrier dysfunction is accompanied by hyperkeratosis of the follicular epithelium. Local follicular deficiency of epidermal lipids (free sterol, ceramides) and increased sebum glycerides may induce abnormal follicular keratinisation. [15]

Certain external chemicals may contribute to comedogenesis. These substances include the ingredients of some cosmetics such as isopropyl myristate, propylene glycol, and D and C red dyes. It has been suggested that the excretion of products from the sebaceous gland occurs through an organized acellular tubular conduit – the sebolemmal sheath produced by the sebaceous duct cells; rupture of this sheath may contribute to comedogenesis. However, this concept has yet to be confirmed by others.

Bacterial Colonisation

Bacterial colonization of sebaceous follicles is another important contributing factor in the production of acne. Propionibacterium acnes, staphylococcus epidermidis and pityrosporum ovale are the primary organisms found in the acne patients but propionibacterium acnes is the most abundant organism present.[16] Ideally for the overproduction of propionibacterium acnes, the anaerobic atmosphere of the blocked sebaceous follicle with its lipids substrate is useful for the production of the free fatty acids, which in turn may be a factor causing retention hyperkeratosis.

The chemotactic factor released by propionibacterium acnes attracts to the follicle. These leucocytes ingests propionibacterium acnes with the resultant release of hydrolytic enzyme that damage the follicular wall causing it to rupture. The content of the follicle provoke inflammatory reaction. The severity of the inflammation in acne [17] is determined also by host response to propionibacterium acnes. Antibodies IgGI, IgG2, IgG3 to propionibacterium may be involved in the pathogenesis of acne.[18]

Mediation of Inflammation

Propionibacterium acnes produce proteases like lipases phosphatases, hyaluranate and lyase which mediate inflammation. This produce biologically active substances that diffuses into the dermis and causes inflammation by activating complement and chemotactic neutrophils.

There is also increasing evidence to support the involvement of toll-like receptors in acne inflammation. Toll receptors recognize ‘abnormal’ organisms. In a way, Propionibacterium acnes can be looked upon as ‘abnormal’ as it is not often present in follicles from subjects without acne. The toll receptors in turn regulate the production of

cytokines which may contribute to acne inflammation. Propionibacterium acnes also produces a prostaglandin-like substance which might be involved, as non-steroidal anti-inflammatory drugs have an anti-acne effect.

Cytokines are known to play a role in inflammatory acne. Ductal corneocytes constitutively produce inter-leukins (including IL-1-α and IL-β and TNF.

Leukotriene precursors are synthesized in the sebaceous gland. LTB4 induces recruitment and activation of neutrophils and monocytes. It also stimulates the production of a number of pro-inflammatory cytokines and mediators that augment and prolong tissue inflammation.[52,53]

EVALUATION OF ACNE LESION

Microcomedone mature and become epithelial lined follicular cyst containing keratinous material, lipid, hair and bacteria.[11] Two types of mature comedones are produced. The open comedone (black head) orifice is widely dilated by a cornified impaction continuous with the deeper keratinized lamella. Black colour is due to melanin and oxidized lipids in the follicle. The closed comedone (white head) is a small usually

flesh coloured papules that has a microscopic opening which keeps its contents from escaping.

CLINICAL MANIFESTATION

The pathognomonic lesion of acne is the comedones, either open or closed. As the disease progress papules, nodules, and cyst may appear as a single lesion or as a combination of all types. As acne lesion, resolve a post inflammatory erythema and even pigmentation can last several months before they resolve.

The deeper inflammatory process, the more likely it will tend to produce permanent scarring which vary from small pits to deep fissures and even hypertrophic or keloidal scar. The primary site of scar is the face and to a lesser degree the back, chest and shoulder. The courses of acne tend to wax and wane. Seasonal variation may be seen.

There are also several subtypes of comedones

Sandpaper Comedones: consists of multiple very small white heads and are found most often on the forehead.

Macrocomedones : are large white heads or black heads greater than 1mm in diameter.

Submarine Comedones : are large comedonal structures greater than 0.5cm in diameter.

Inflammatory lesions may be superficial or deep. The superficial lesions are papules and pustules and the deep lesions are deep pustules and nodules.

Nodules more frequently occur in males. Nodules and deep pustules may lead on to devastating cosmetic effects and scarring.

Scars may show increased collagen. E.g. hypertrophic scars and keloids or be associated with loss of collagen.

i.e. Ice pick scars

Depressed fibrotic scars

Atrophic macules

Perifollicular elastolysis.

GRADING OF ACNE

The severity of acne can be graded on clinical grounds as [19]

Grade 1 (Mild) : Comedones, Occasional, Papule

Grade 2 (Moderate): Papules, comedones, few pustules

Grade 3 (Severe) : Predominant pustules, nodules & abscesses

Grade 4(Cystic) : Mainly cysts, abscess and widespread scarring

Various grading and scoring system in acne : [20]

MODIFIED COOKS METHOD

Reliable method since photographic reference standard is required. Used only for facial lesion. Grading ranging from 0-9 is used for one group that includes comedones papules and macules.[21]

Overall severity is graded on another scale of 0-8 that also includes pustules, nodules and cysts.

LEEDS TECHNIQUE

Complex scores but also includes assessment of lesions over face as well as over back and chest. No photographic reference is required. Face is divided into right and left halves and counting is done on both sides.[22]

SEVERITY INDEX MICHAELSON

Simple score, by counting number of open or closed comedones, papules, pustles and infiltrated lesions. Severity index. 5 for comedones, 1 for papule, 2 for pustle, 3 for infiltrated lesions, 4 for cystic lesions [23]. The total number of lesions including the comedones, papules and pustules were counted before the start of treatment and the response noted by the reduction of the number of total lesions and graded.

PHYSIOLOGICAL & ENVIRONMENTAL FACTORS THAT INFLUENCE ACNE

DIET

A potential role for diet in acne is controversial. That natural hormonal components of milk and / or other bioactive molecules in milk could exacerbate acne.

High glycemic index, which in turn can trigger insulin and insulin like growth factor that influence androgens and retinoids. This could thereby induce seborrhoea, comedones and acne.

The trend of increased weight among children and earlier puberty may be reflected in early clinical acne.[24]

Premenstrual Flare

Possibly it is related to a premenstrual change in the hydration of the pilosebaceous epithelium. Progesterone and oestrogen also have both pro and anti inflammatory effects.[25]

Sweating

Sweating causes a detoriation in their acne. Ductal hydration may be the responsible factor.[26]

Ultraviolet Radiation

UV radiation may enhance the comedogenicity of sebum.[27]

Occupation

Hydration of the ductal stratun corneum may induce acne in such occupations as catering and steam cleaning. Patients dealing with oil may develop an acneiform oil folliculitis.[26]

Smoking and Acne

One study has shown a linear relationship between acne prevalence and the number of cigarettes smoked daily.[28]

Stress

Emotional factors presumably affect acne by altering the adrenal pituitary axis.[29]

UNCOMMON ASSOCIATIONS WITH ACNE

Acne excoriee

Apert's syndrome

Body dysmorphic disorder and acne

Darier's disease

Folliculitis on the scalp

Scalp folliculitis

Folliculitis decalvans

Dissecting folliculitis of the scalp

Granulomatous / lymphoedematous acne

Hidradenitis suppurativa

Other forms of Acne

- Drug induced acne / acneiform eruptions
- Endocrine acne
- Externally induced acne
  - Cosmetic acne
  - Pomade acne
  - Detergent acne
- Infantile and Juvenile acne
- Mechanical acne
- Occupational acne
  - Oil and tar acne
  - Chloracne
- Solar comedone
- Tropical acne

DRUGS REPORTED TO CAUSE ACNE / ACNE LIKE ERUPTIONS

Hormones and steroids

Gonadotrophins, Androgens, Anabolic Steroids and Oral and topical steroids

Halogens

Bromides, Iodides and Halothane

Antiepileptic Drug

Phenytoin, Phenobarbitone and Troxidone

Anti-tuberculous Drugs

Isoniazid and Rifampicin

Miscellaneous

Chloral hydrate, Cyanocobalamin, Disulfirum, Lithium, Psoralens, Quinine, Thiourea, Thiouracil and Sulphur

ENDOCRINE ACNE

The endocrine diseases associated with acne [30]

Cushing's disease

Late onset congenital adrenogenital syndrome

Polycystic ovarian syndrome

Adrenal / ovarian tumour

An endocrine evaluation may be indicated for adult females

With sudden onset of severe acne

In the presence of hirsutism

Irregular menstrual periods

Other signs of hyperandrogenism

Relapse shortly after starting isotretinoin therapy.

INVESTIGATIONS TO RULE OUT ENDOCRINE ACNE

- Serum dehydroepiandrosterone sulphate (DHEAS) >21.7μmol/lt – adrenal tumour.
- Congenital adrenal hyperplasia – DHEAS between 10.8-21.7μmol/lt.

  17α hydroxyprogesterone > 12-8μmol/lt and cortisol level increased .
- Serum Total testosterone increased in the range of 520-700μmol/lt and increased LH- FSH ratio > 2-3 in polycystic ovarian disease
- Serum testosterone very much elevated in case of ovarian tumour
- An ultrasound abdomen – to rule out PCOD[30]

INFANTILE AND JUVENILE ACNE

Infantile and Juvenile Acne, which mainly affects males present as facial acne in children between 3 and 24 months, and may last upto 5 years of age.

The individual lesions include comedones, papules, pustules, nodules and scarring. Infantile acne is very rarely associated with other clinical features of androgen excess such as hirsutism or premature closure of epiphyses; very occasionally, there may be transient or more persistent high plasma levels of testosterone, LHs and FSHs. An associated virilizing tumour or underlying congenital adrenal hyperplasia is extremely rare. If the child is otherwise well and there are no other abnormal features, no endocrine investigations are required. However, such investigations may be appropriate in a patient who develops acne between 5 and 8 years of age.

Severe Acne Variants

Acne conglobata

Acne fulminans

Gram Negative Folliculitis

Pyoderma faciale

Vasculitic / Pyoderma gangrenosum acne

SYNDROMES ASSOCIATED WITH ACNE

SAHA SYNDROME

Seborrhoea, Acne, Hirsutism and Alopecia

SAPHO SYNDROME

Synovitis, Acne, Pustulosis, Hyperostosis and Osteitis

APERTS SYNDROME

Early epiphyseal closure, Hypertelorism, Flattened occiput, Proptosis (due to shallow orbits), Prognathism, Parrot beaked nose and Fused shortened digits

TREATMENT FOR ACNE VULGARIS

Choice of Topical Treatment

Predominantly Anticomedonal

Adapalene, All-trans-retinoic acid, Azaleic acid and Isotretinoin

Predominantly Antimicrobial

Azaleic acid, Benzamycin, Benzoyl peroxide, Clindamycin, Erythromycin and Tetracycline

Predominantly Anti-inflammatory

Adapalene, Nicotinamide, Topical Antibiotics

ORAL THERAPY

Oral Antibiotics

Tetracycline, Oxytetracycline, Doxycycline, Minocycline and Azithromycin

Hormonal Treatments

Predisolone plus oestrogen, Oestrogens plus antiandrogens, Spironolactone

Oral Retinoid

Isotretinoin

Other Oral Treatment

Oral zinc, Non steroidal anti inflammatory drugs and Oral Vitamin A

Treatment of Scars

Scar excision, Dermabrasion and laser resurfacing, Collagen Injection, Gelatin Matrix implant, Chemical Peeling and Cosmetic Camouflage

TOPICAL TREATMENT OF ACNE

Patients with mild acne will do well with only topical treatment; those with more severe and recalcitrant acne will require systemic medication. The ideal acne treatment would be entirely topical to avoid systemic effects. It would reduce abnormal keratinization, inhibit sebum production, and limit the production and activity of Propionibacterium acnes. [31]

Tretinoin

Since the pioneer study by Kligman et al. in 1969, topical tretinoin has become a standard agent in the treatment of acne. Although the exact mode of action of tretinoin is unknown, current evidence suggests that topical tretinoin decreases cohesiveness of follicular epithelial cells with decreased microcomedone formation. Additinally, tretinoin stimulates mitotic activity and increased turnover of follicular epithelial cells causing extrusion of the comedones. This in turn reduces the number of inflammatory lesions resulting from the eventual rupture of the micro comedones. [31, 32]

Side Effects

Mild erythema, Peeling, Severe dryness, Local irritation and photodermatitis

Topical Isotretinoin

Topical isotretinoin was developed as a safer alternative to the oral medication. Although effective in mild to moderate inflammatory and non inflammatory lesions, it works only by affecting abnormal follicular keratinization. It has no effect on sebum production. [32, 33]

Adapalene

Adapalene is a synthetic derivative of naphthoic acid with retinoid-like activity. Adapalene is a modulator of cellular differentiation, keratinization, and inflammatory processes suggesting that its therapeutic role is both as a comedolytic agent as well as an anti-inflammatory agent.

Tazarotene

It has bene shown to be effective in an active treatment for inflammatory and non-inflammatory lesions, especially with stubborn comedones.

Salicylic Acid

Salicylic acid is effective against comedones and inflammatory lesions in acne vulgaris. It represents a useful but less effective option for patients unable to moderate treatment with tretinoin, because its comedolytic activity is only approximately 25% that of tretinoin.[34]

TOPICAL ANTIMICROBIALS

Benzoyl Peroxide

Benzoyl peroxide is a powerful oxidizing agent and antimicrobial that works by decreasing the population of Propionibacterium acnes. It is

most effective for inflammatory acne consisting of papules and pustules. Clinical studies show a modest reduction in comedones, probably as an indirect effect. [35]

Side Effects

Irritation, Redness and Scaling

Topical Antibiotics

Topical antibiotics are most useful in the management of mild inflammatory acne. They can be the initial treatment modality or used as a adjunct to treatment with tretinoin or benzoyl peroxide. Bacteriostatic antibiotics are thought to improve acne by decreasing the formation of by-products, but not necessarily the actual number of Propionibacterium acnes. Sublethal levels of antibiotic are able to reduce the promotion of chemotactic factors by Propionibacterium acnes that play an important role in the disruption of chemotactic factors and the promotion of subsequent inflammation. Papular and pustular acne respond best with topical antibiotics.[37]

Topical Azelaic Acid

Patient with predominantly inflamed lesions should received topical azelaic acid, benzoyl peroxide or topical antibiotics.[36, 37]

MISCELLANEOUS TOPICALS

Nicotinamide, Drying and Peeling Agents

COMBINATION THERAPY

Because of acne's multifactorial orgins, most patients respond better if therapy encompasses more than one area of pathophysiology. Combination therapy is therefore rational and effective,

The efficacy of benzoyl peroxide and topical antibiotics may be increased by concurrent therapy with tretinoin, because tretionin increases the cutaneous penetration of other topically applied agents. Benzoyl peroxide and topical antibiotics may exert a synergistic antimicrobial effect when used together; a preparation consisting of 3% erythromycin and 5% benzoyl peroxide in a gel base is more effective in the improvement of inflammatory acne than either agent alone.

Treatment of inflammatory acne with a sequential regimen of topical tretinoin and BP/erythromycin gives good response. [36, 37]

TOPICAL RETINOIDS

INTRODUCTION

In topical preparation, retinoid are widely used as prescription drugs as well as cosmeceuticals.

In 1976, Michael Sporn and his colleagues originally defined retinoids as both the naturally occurring compounds with Vitamin A activity and the synthetic analogues of retinoid.[38]

Now retinoid is defined as any molecule that, by itself at or through metabolic conversion, binds to and activate the retinoic acid receptors.

Topical retinoid have been used in acne therapy since 1962 and the first substance to be studied was tretinoin. Their biological effects are mediated and regulated by nuclear hormone receptors (Retinoid acid receptors (RAR), retinoid X receptor (RXR) and cytosolic binding proteins. Each receptor family includes, three subtypes (α, β, γ) that induce expression or down regulation of target genes in a ligand dependent manner.[39]

HISTORY

The history of the development of retinoids in dermatology comprised of three generations. The first is **nonaromatic retinoids**, which include tretinoin – (retinoic acid) and isotretinoin (13 cis retinoic acid). Both can be used as topical or systemic treatment.[39]

The second generation retinoids are **monoaromatic** retinoids etretinate and its metabolite acitrolin, which are only effective as a systemic treatment. The third generation retinoids are **polyaromatics** i.e. adapalene, tazarotene δ Baxorotene.

The most studied retinoids for topical acne treatment worldwide are tretinoin and adapalene. Depending on country and indication tazarotene, isotretinoin, motretinide, retinoide β glucunonide and retinaldehyde are also available for acne treatment.[40]

RETINOID RECEPTORS

The discovery and characterization of retinoic and receptors (RARs) as having molecular features that are similar to steroid / thyroid hormone receptors were land mark findings.

They bind to regulatory regions in DNA called hormone response elements or target sequences and activate gene transcription in a ligand dependent manner.

Human epidermis expresses RAR α, RAR γ, RXRα. RXR β, messenger RNAS.

There relative levels of retinoid receptor and MRNAS mirror their relative protein levels.

For RAR proteins 87% are RAR γ, and 13% are RAR α with no detectable RARβ of the RXR proteins, 90% are RXR α. [41]

RECEPTOR SELECTIVE RETINOIDS

Synthetic molecules could be screened for their ability to bind to and activate specific receptors.

Many of these compounds still considered as retinoids by virtue of their ability to activate the receptors.

Adapalene has restricted receptor specificity possessing poor affinity for RAR-α , higher affinity for RAR-β & γ, and no interaction with RXR-α. Tazarotene cannot directly binds to RARS or RXRs. Its metabolite, tazarotenic acid has receptor selectivity for RARS. [42]

MECHANISM OF ACTION

Retinoid action are mediated by retinoid receptors. RARs are transcription factors, so the skin effects of retinoids must be through regulated gene expression.

The best mechanism is activation of retinoid target genes through direct binding to retinoic acid responsive elements (RARE) in the gene promotion thereby stimulating the basal transcriptional machinery.

RARE regulated genes will be identified that encode for proteins that function to modulate cutaneous growth and differentiation. These protein products activate other non-RARE containing genes to produce the clinical features of retinoid action in skin.[41, 42]

CELLULAR METABOLISM OF NATURAL RETINOIDS AND MOLECULAR MECHANISM OF RETINOID SPECIFIC GENE ACTIVATION

Retinoid delivered to a cell is bound to cellular retinoid binding protein 1 (CRBP). Retinoid can be esterified, via lecithins: retinol acyl transferace (LRAT) and stored as retinoid esters.

Hydrolysis of retinol ester by its hydrolase yields free retinol.

Sequential oxidation of retinol generates retinoid acid which is bound to cellular retinoic acid binding protein (CRABP). All trans

retinoic acid can be isomorized to 9 cis retinoic acid. Hydroxylation of transretinoic acid by cytochrome P 450 enzyme CYP 26 generates 4 hydroxy retinoic acid which is inactive.

In human skin, RAR α and RXR α heterodimers bound to RARE – response elements and transduce retinoid effects in the presence of RAR ligands. [41, 42]

MOLECULAR MECHANISM OF RETINOID INDUCED EPIDERMAL HYPERPLASIA

Topical retinoid activates RAR/RXY heterodimers in suprabasal keratinocytes, causing activation of transcription factors.

Heparin binding epidermal growth factor and amphiregulin are activated, and this leads to proliferation of basal keratinocytes thickened epidermis and peeling / flaking of the stratum corneum.

MECHANISM OF TOPICAL RETINOID IN ACNE VULGARIS

Retinoids influence the proliferation and differentiation of cells and therefore reverse the abnormal desquamation by affecting the follicular epithelial turnover. This leads to expulsion of mature comedones (open and closed type) and suppression of microcomedone formation. [42, 44]

The change of microclimate in the pilosebaceous follicle by prevention of hyperconification promotes an inhospitable aerobic environment for P acnes and is likely to enhance the penetration of other topical drugs.

An indirect immunomodulatory effect takes place by changing the follicular environment and also has anti-inflammatory effect.

Another benefit of topical retinoids is their ability to reduce post inflammatory hyperpigmentation.

Retinoids are especially suitable for maintenance treatment because of their multifactorial antiacne efficacy without undesirable effects during long term treatment and their ability to prevent micro comedone formation.

Concerning safety precautions, one has to be aware that topical retinoid therapy has not been established in patients younger that 12 years and women of child bearing age need to be warned of the potential risk of teratogonicity and recommended adequate birth control measures.[45]

The effect of a retinoid topically applied on the skin is dependent on the stability of the substance, its ability for tissue penetration, the cellular uptake and the intracellular metabolism.

Topical retinoid alone or in combinations are regarded today as first line treatment for both comedogenic and inflammatory acne.

CLINICAL USE OF TOPICAL RETINOIDS [45]

Approved Indications	:	Acnevulgaris
		Psoriasis
		Photoaged Skin
Unapproved Indication	:	Post inflammatory hyperpigmentation
		Melasma
		Early stretch marks
		Cosmetic Indication
		Actinic Keratoses

Adverse effect of topical retinoids

Skin irritation, Xerosis, scaling, Itching, Erythema, Peeling

Uses of Topical Retinoids

Tretinoin	;	Mild / Moderate acne
		Photoaging
		Biological skin aging
Isotretinoin	:	Mild / Moderate acne

Aliretinoin	:	AIDS related Kaposi's sarcoma
Motretinide	:	Mild / Moderate Acne
Adapalene	:	Mild / Moderate Acne
Tazarotene	:	Mild / Moderate Acne
Retinol	:	Cosmetic Indications
Retinol Palmitate	:	Cosmetic Indications
Retinaldehyde	:	Cosmetic Indication

ADAPALENE

Adapalene a naphthoic acid is a third generation retinoid

Adapalene was approved in 1996 by the U.S. Food and Drug Administration for use in the treatment of acnevulgaris.[48]

MECHANISM OF ACTION

The drug respectively interacts with only the 6 and 9 sub types of the nuclear retinoic acid receptors (RARS). This is in contrast to the 1st generation retinoid, tretinoin which binds for all RARS and also to cytosolic retinoic acid binding protein (CRABP)

Selective binding of adalapalene to retinoic acid receptors is believed to contribute to its lesser capacity to cause irritation and greater patient acceptability.[48]

Adapalene has been demonstrated to penetrate the sebaceous follicles within five minutes of its application on the skin.

Adapalene has rapid onset of action and a particularly favourable tolerability profile compared with other retinoids.

Adapalene is therefore assured of a role in the first line treatment of acne vulgaris.

Some additional properties such as increased chemical and light stability rigidity, and high lipophilicity are purported to cause reduced risk of photo-instability and local skin irritation, possibly enhancing compliance.

EFFECTS ON CELLULAR DIFERENTIATION AND PROLIFERATION

Although the exact mode of action of adapalene is unknown, it is suggested that topical adapalene may normalize the differentiation of follicular epithelial cells resulting in decreased microcomedone formation. It is thus, a modular of cellular differentiation, keratinization, and inflammatory processes, all of which represent important features in the pathology of acne vulgaris. Adapalene has restricted receptor

specificity possessing, higher affinity for RARβ and RAR λ and poor affinity for RAR α. [49]

COMEDOLYTIC EFFECT

It causes a dose related reduction in the number of comedones and an increase in comedone profile and epidermal thickness.

ANFI-INFLAMMATORY EFFECTS

Adapalene causes 5 – and 15-lipoxygenase activity inhibition and cyclooxygenase inhibition (100 times less than lipoxygenase inhibition). These effects have been demonstrated in vitro and in-vivo.

PHARMACOKINETICS

Absorption through human skin is low. Only trace amounts (<0.25ng/ml) of parent substance have been found in the plasma of acne patients following chronic topical application of adapalene in controlled clinical trials. Adapalene is very stable on the skin. In the gel formulation, restriction on particle size to 3-10m has been shown to optimize delivery to the pilo-sebaceous unit. Very little drug penetrates the skin, and that which does remains mainly in the epidermis, with some progressing to the dermis. Absorbed drug has a half life of about 13 hours.[49]

DOSAGE AND ADMINISTRATION

Adapalene applied once a day to affected areas after washing the face before retiring to bed. A thin film of the adapalene should be applied, avoiding eyes, lips, and mucous membranes. During the early weeks of therapy, an apparent exacerbation of acne may occur due to the action of the medication on previously unseen lesions and should not be considered a reason to discontinue therapy. Therapeutic results would be noticed after eight to twelve weeks of treatment.[48]

ADVERSE REACTIONS

Erythema, scaling, dryness, pruritus, and burning will occur in 10-40% of patients. Pruritus or burning immediately after application also occurs in approximately 20% of patients. Approximately 1% or less of patients seen with skin irritation, burning / stinging, erythema, sunburn, and acne flares. These are most commonly seen during the first month of therapy and decrease in frequency and severity thereafter. All adverse effects are reversible upon discontinuation of therapy.[49]

DRUG INTERACTIONS

Concomitant use of other potentially irritating topical products (medicated or abrasive soaps and cleaners, soaps and cosmetics that have

a strong drying effect, and products with high concentrations of alcohol, astringents, spices or lime) should be approached with caution as ADAPALENE has the potential to produce local irritation in some patients.

Caution should be exercised in using preparations containing sulfur, resorcinol, or salicylic acid in combination with ADAPALENE, if these preparations have been used it is advisable not to start therapy with ADAPALENE until the effects of such preparations in the skin have subsided.

OVERDOSAGE

ADAPALENE is intended for cutaneous use only. If the medication is applied excessively, marked redness, peeling, or discomfort may occur.

CONTRAINDICATIONS

Hypersensitivity to adapalene or any of the components in the vehicle gel.

PRECAUTIONS

General

Exposure to sunlight should be minimized.

Use of sunscreen products and protective clothing is recommended when exposure cannot be avoided.

Avoid contact with eyes, lips, angles of the nose, and mucous membranes. The product should not be applied to cuts, abrasions, eczematous skin, or sunburned skin.

Certain cutaneous signs and symptoms such as erythema, dryness, scaling, burning, or pruritus may be experienced. These are most likely to occur during the first two to four weeks and will usually lessen with continued use of the medication.

PREGNANCY

Adapalene should not be used during pregnancy.

NURSING MOTHERS

Caution should be exercised when Adapalene is administered to a nursing woman.[48]

PAEDIATRIC USE

Safety and effectiveness in paediatric patients below the age of 12 have not been established.[48]

TAZAROTENE

It is a receptor selective retinoid. Tazarotene is a synthetic acetylonic retinoid that penetrates the skin and is converted to an active metabolite, tazarotenic acid.

Mechanism of Action

It is a receptor selective retinoid, efficacious in the treatment of patients with acne vulgaris.

Tazarotene itself does not bind to retinoic acid receptors (RADs), however tazarotenic acid binds with high affinity to the RARs with the rank under of affinity being RARβ>RARα > RARγ. It is effective in reducing inflammatory lesions as well as non-inflammatory lesions. It normalizes keratinocyte differentiation, reverses keratinocyte hyperproliferation. Reduction in comedone counts was greatest when tazarotene 0.1% was used as first line therapy.[49]

Mode of Application

In the treatment of facial acne, patients are instructed to apply a thin film to cover the entire face. It is important to treat the entire face in order to treat and prevent microcomedone formation.

Tazarotene is initially applied for 2 minutes, then washed off with soap and water. The time can be increased by 1 minute every 3 days to a

maximum of 5 minutes as tolerated. The contact time is reduced to 3 minutes if irritation occurs, then gradually increased to 5 minutes as tolerated.

SIDE EFFECTS

Skin irritation, Peeling, Erythema, Dryness, Burning and Itching

They are most common during the first 1-2 weeks of therapy and can be minimized with use of cream formulation, alternate day application.

Contra Indications

Children under 12 years of age, Nursing Women, Pregnancy, Hypersensitivity to tazarotene or any of the components in the vehicle.

Of the different clauses antiacne medications, retinoids are thought to be the best, because the only agent to normalize the abnormal follicular epithelial differentiation / desquamation viewed to be in the pathogensis of acne lesions. [49, 50, 51]

AIM OF THE STUDY

The aim of the study is to compare the efficacy of topical adapalene and topical tazarotene in the treatment of acne vulgaris with each other.

The agents compared were the following:-

1) 0.1% Adapalene cream
2) 0.1% Tazarotene Cream

MATERIALS AND METHODS

One hundred patients of either sex were enrolled and randomly assigned for the above study. The study was singleblind randomized open prospective comparative clinical trial. It was carried in the Department of Dermatology, Government General Hospital, Chennai during the period of August 2006 to August 2008.

Inclusion Criteria

Patients of either sex with mild to moderate acne vulgaris

Exclusion Criteria

Pregnant and Lactating Women

Drug induced Acneform eruptions.

Drug allergy

Children less than 12 years

Treatment Protocol and Methodology

- Patients selected were informed about the nature of study and consent was obtained from them.

- The demographic datas such as age and sex of the selected patients, occupation, marital status and duration of the disease were taken.
- Other histories like family history of acne, past and present history of topical and systemic treatments were noted and patients were advised to avoid other treatments for acne.
- The precipitating factors for acne such as premenstrual flare, summer exacerbation and stress were noted. History of smoking also was noted.
- The other features of hyperandrogenism such as irregular menstruation, oligomeorrhoea and hirsutism were noted .
- Patients were subjected for general and systemic examination. A thorough dermatological examination was done and other existing dermatological lesions apart from acne were recorded.
- Number of comedones, papules and pustules counted and graded.
- The 100 patients who fulfilled the inclusion criteria were selected randomly and assigned into two groups.

  Ist Group - Adapalene 0.1% Cream

  IInd Group - Tazarotene 0.1% Cream

- Clinical photographs of the lesions were taken before commencement of therapy and after completion of therapy.
- Patients were instructed to review for every two weeks and report the severe side effects, if any, immediately.
- Married female patients were advised oral contraceptive therapy during this treatment.
- The aforesaid study was conducted for 12 weeks.

Method of Application

The patients were advised to avoid cosmetics and other topical application over the face.

Group - I

0.1% adapalene cream

Adapalene applied once a day over the entire face before retiring to bed. After washing the face, patient was advised to apply a thin film of the adapalene cream, avoiding contact with eyes, lips and mucous membrane. Adapalene was initially applied for an hour then washed off with soap and water. The time can be increased gradually, can be applied overnight if there is no irritation or any other adverse effect.

Group – II

0.1% Tazarotene Cream

Tazarotene applied once a day over the entire face before retiring to bed. After washing the face, patients were advised to apply the tazarotene cream initially for 2 minutes then washed off with soap and water. The time can be increased gradually upto 5 minutes. If the irritation is very severe the duration should be reduced to 3 minutes. During application, contact with eyes, lips and mucous membrane should be avoided.

For both the groups patients were instructed about the side effects of topical retinoids such as dryness, erythema, skin irritation, skin peeling and itching. Patients were reviewed every two weeks and report the severe side effects, if any, immediately.

During each visit, the response to the therapy and side effects were noted. Patients were also instructed to avoid sun exposure by using sun protective measures .

OBSERVATIONS

The following observations were made in the present study. Among the 100 patients under study, 65 were males, 35 were females. They were in the age group ranging from 15 years to 29 years. 73 patients were students, others were employees and housewives.

The duration of acne ranged from 6 months to 8 years with a mean of 17 months.

31% of patients had family history of acne. The following precipitating factors were recorded as per history from the patient.

- Premenstrual flareup was noted in 15% patients.
- Summer Exacerbation in 23% of patients.
- 35% patients were associated with stress, such as education and unemployment.
- 30% of patients had associated history of smoking.

History of previous topical application was present in 30% of patients. The time interval between the last and present topical therapy was between 6 months to 3 years. 10% of patients had treatment with

systemic antibiotics. None of them had systemic retinoid treatment. Details of topical application were not available with some patients .

Of the 100 patients 38 patients had Grade I acne and 62 patients had Grade II acne.The dermatological conditions associated with acne in this study were

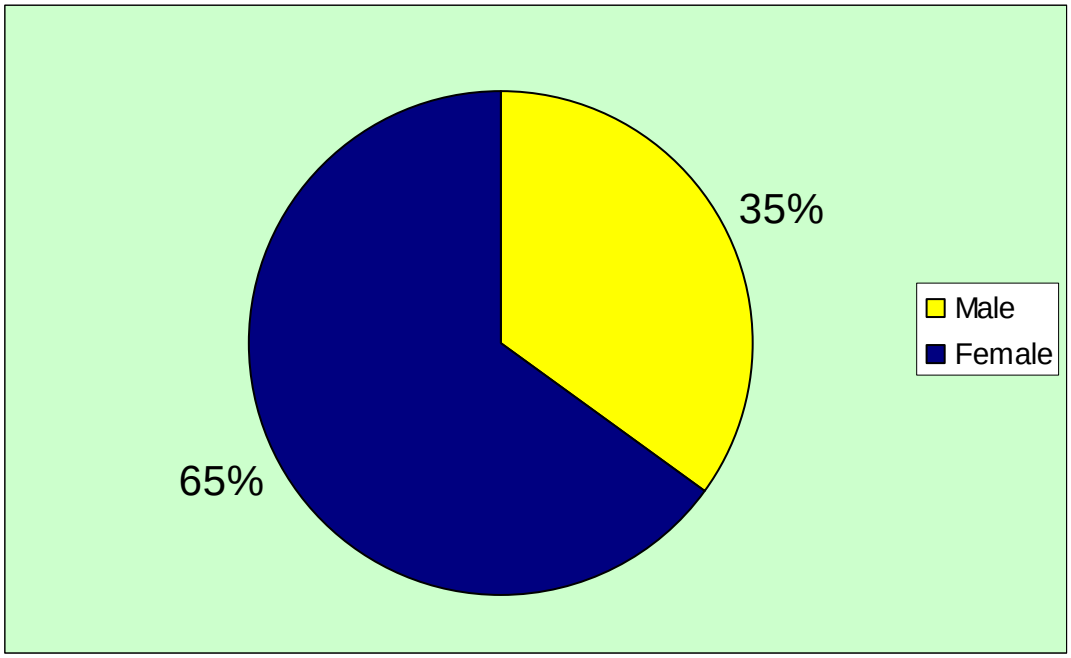
Tinea Versicolor, Vitiligo, Polymorphic light eruption and Seborrhoeic dermatitis

SEX DISTRIBUTION

Male	Female
65%	35%

In this study, Acne vulgaris showed increased prevalence among males.

SEX DISTRIBUTION

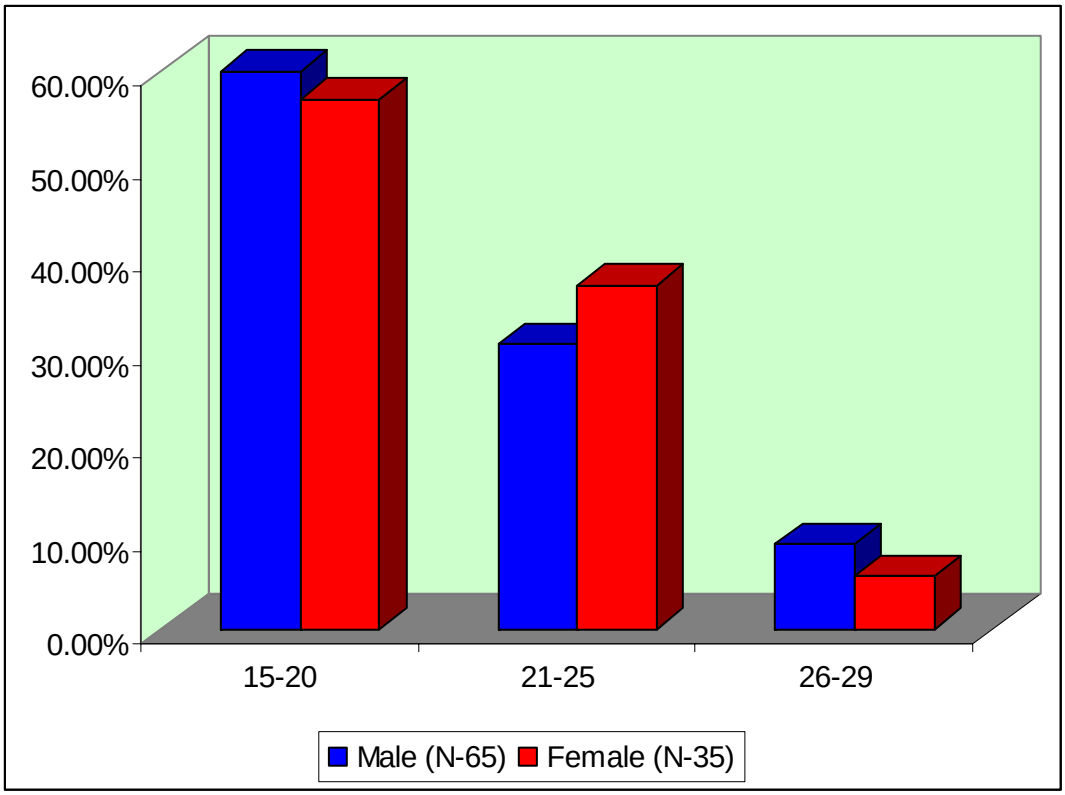


AGE DISTRIBUTION

Age	Male (N-65)	%	Female (N-35)	%
15-20	39	60%	20	57%
21-25	20	30.7%	13	37%
26-29	6	9.2%	2	5.7%

Regarding age distribution , the increased prevalence was noted in the age group of 15 to 20 years irrespective of sex.

AGE DISTRIBUTION

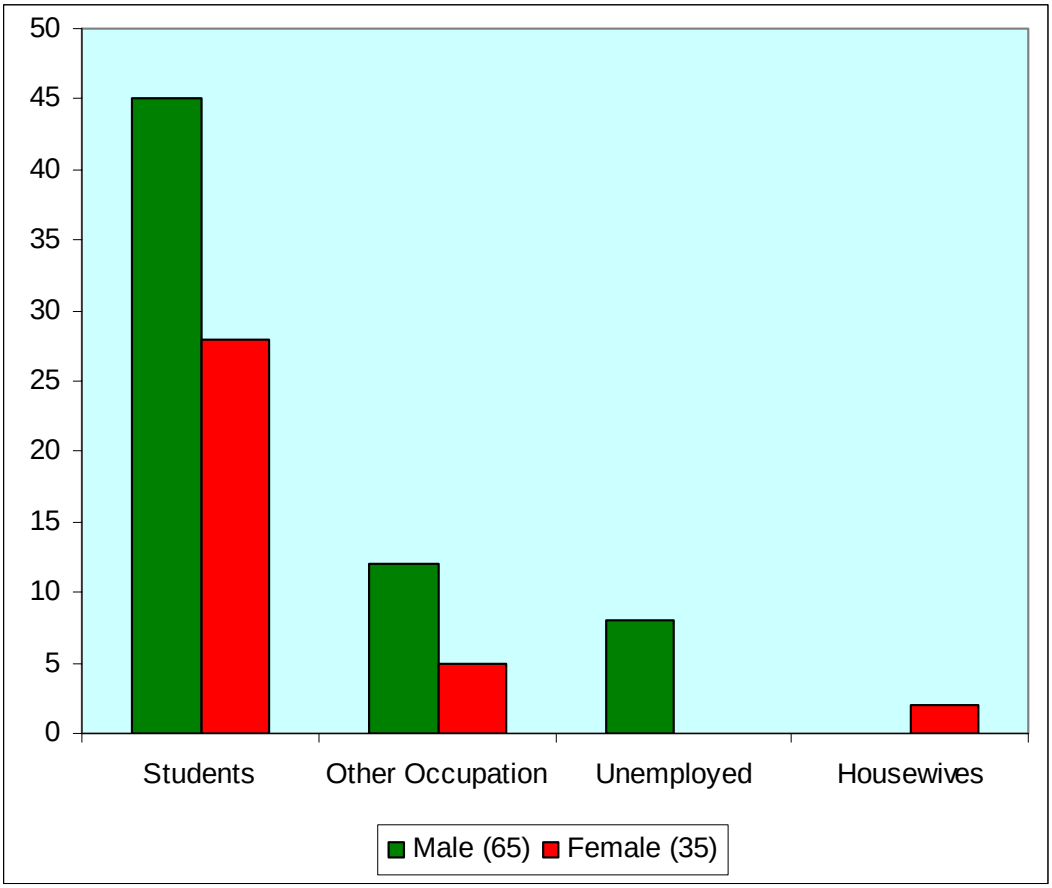


THE **FOLLOWING OBSERVATIONS** WERE MADE IN THIS STUDY

	Male (65)	**Female (35)**
Students	45	28
Other Occupation	12	5
Unemployed	8	-
Housewives	-	2

In the above study, pronounced incidence of acne vulgaris was noted among students.

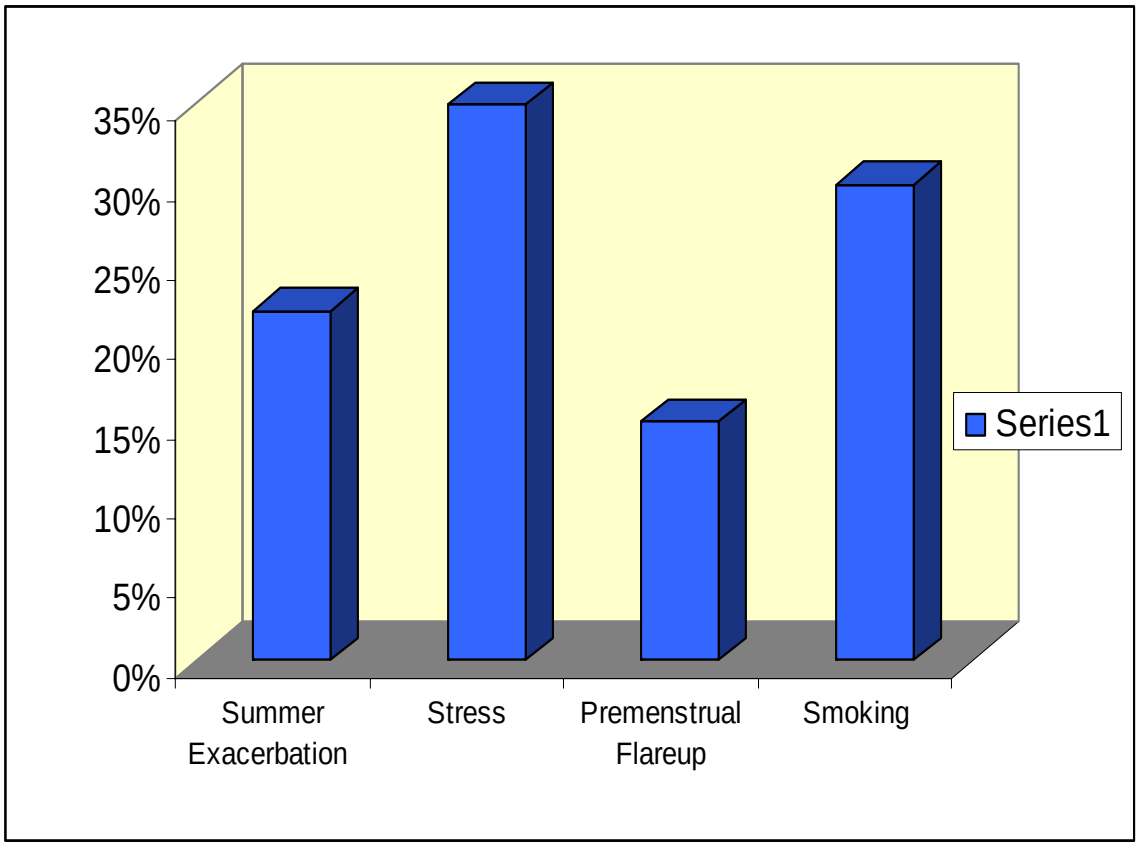
OCCUPATIONAL STATUS



PRECIPITATING FACTORS ASSOCIATED WITH ACNE VULGARIS
(IN PERCENTAGE)

	Male	**Female**
Summer Exacerbation	15	8
Stress	20	15
Premenstrual Flare	-	15
Smoking	30	

PRECIPITATING FACTORS



ASSOCIATED OTHER SKIN DISORDERS WITH ACNE VULGARIS

Diseases	Male (n)	Female (n)
Pityriasis versicolor	4	2
vitiligo	2	-
Polymorphic light eruption	5	4
Seborrhoeic dermatitis	7	2

The therapeutic response observed in patients treated with topical adapalene (0.1% cream)

There was moderate to good response following treatment with adapalene(0.1% cream). After about 6 weeks the total number of lesions came down to 42%. At the end of 8 weeks 60% of the lesions subsided. At the end of 12 weeks, the overall reduction rate was 80.3%.

TABLE – I

Observation of responses with topical adapalene in Group I patients with acne (N-50)

	Average number of lesions (weeks)							**Average number of lesions reduced**	**Percentage Reduction**
	0	**2**	**4**	**6**	**8**	**10**	**12**		
Comedones	8.2	7.0	6.1	5.0	3.8	2.8	2.2	6.0	73.1%
Papules	5.3	5.0	4.8	3.6	2.2	1.4	0.8	4.5	84.9%
Pustules	1.8	1.0	0.6	0.2	0.0	0.0	0.0	1.8	100%
Total Lesions	15.3	13.0	11.5	8.8	6.0	4.2	3.0	12.3	80.3%

The therapeutic response observed in patients who have been treated with topical tazarotene(0.1% cream)

	Average number of lesions (weeks)							Average number of lesions reduced	% Reduction
	0	**2**	**4**	**6**	**8**	**10**	**12**		
Comedones	8.4	8.0	7.6	6.4	5.8	5.0	4.1	4.3	51.1
Papules	4.6	4.0	4.0	3.6	3.4	3.3	2.1	2.5	50.40
Pustules	0.5	0.5	0.5	0	0	0	0	0.5	100.00
Total Lesions	13.5	12.5	12.1	10.0	9.2	8.3	6.2	7.3	54.07

This study shows, there was a mild improvement with topical tazarotene cream application. After about 4 weeks, the percentage reduction was 7.70% only. At the end of 8 weeks the reduction rate was 29.8%. At the end of 12 weeks the over all reduction rate was 54.07%.

The therapeutic response according to Age Group

Group - I

TOPICAL ADAPALENE 0.1% Cream

Age Group	Response		
	Mild	Moderate	Good
15-20		13	15
21-25		4	9
26-29		2	7

Group - II

TOPICAL TAZAROTENE 0.1% Cream

Age Group	Response		
	Mild	Moderate	Good
15-20	2	11	2
21-25	8	4	1
26-29	7	2	-

In this study, both Group – I & II patients showed moderate to good response in the age group of 15-20 years.

COMPLICATIONS

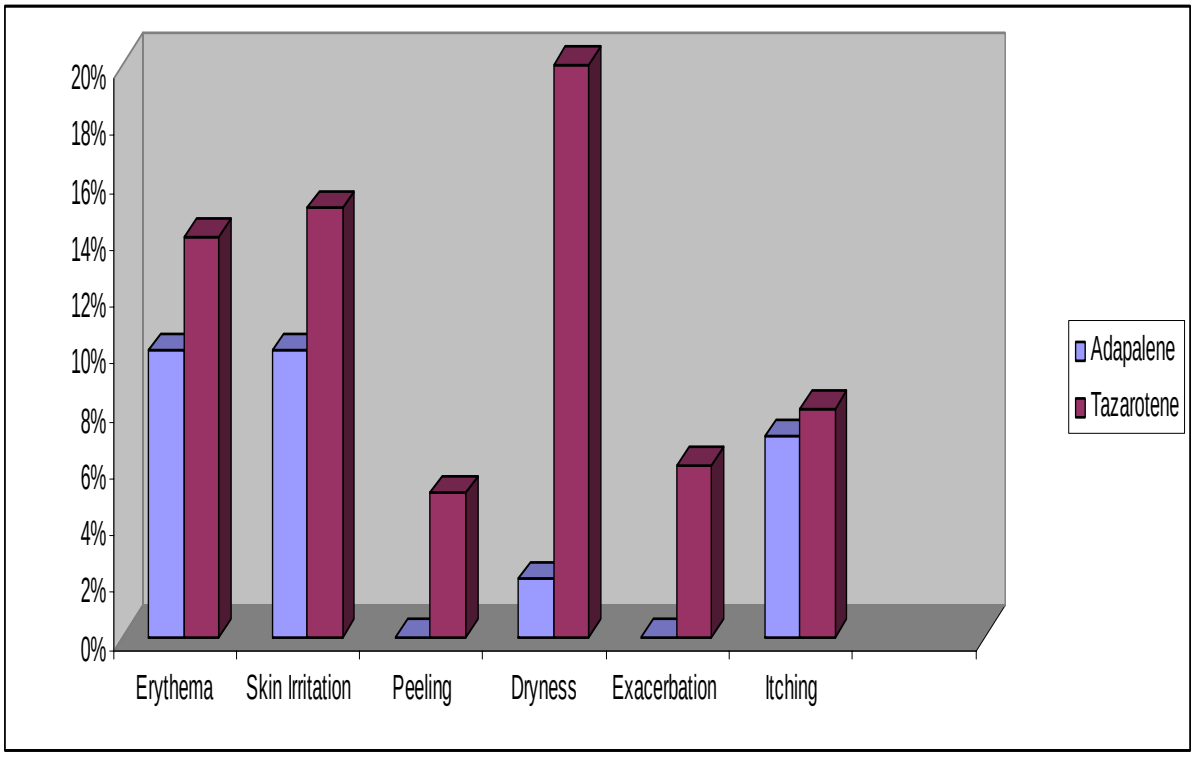
During the treatment with topical 0.1% adaplene cream , the side effects observed were minimal and it was transient for a short period. More common side effects observed with this treatment were erythema, dryness, skin irritation and itching.

Treatment with topical tazarotene showed severe and long lasting erythema and skin peeling leading to poor patient compliance . Because of the severe side effects with topical tazarotene, the duration of daily topical application was restricted to 3 minutes only.

Side effects observed during therapy

Side Effects	Group – I Adapalene 0.1%	Group – II Tazarotene 0.1%
Erythema	10	14
Skin burning	10	15
Peeling		5
Dryness	2	20
Exacerbation	6	-
Itching	7	8
Infections	-	-

SIDE EFFECTS



The response following the therapy for both Group I & II

Nil : 0 to 25% reduction of acne lesions

Mild : 26 to 50% reduction of acne lesions

Moderate : 51 to 75% reduction of acne lesions

Good : 76 to 100% reduction of acne lesions

Response	**Adapalene 0.1% Cream**	**Tazarotene 0.1% Cream**
Nil	-	3
Mild	-	27
Moderate	19	17
Good	31	3

According to this study , of the patients treated with 0.1% adaplene cream , 19% of the patients showed moderate response and 31% showed good response.

According to this study , of the patients treated with 0.1% topical tazarotene cream, 27% of the patients showed mild response, 17% with moderate response and 3% showed good response.

Comparison of patients treated with topical adapalene and topical tazarotene (average number of lesions)

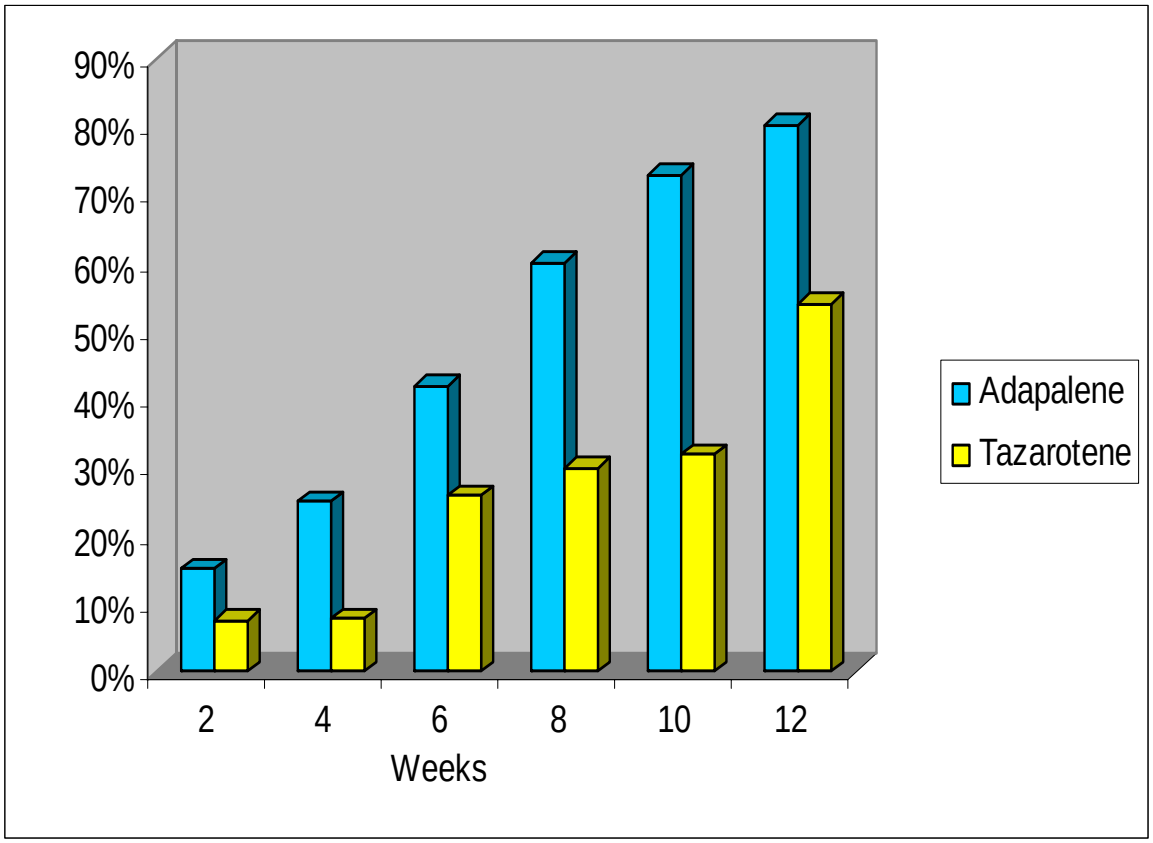
Weeks	Adapalene	Tazarotene <13.5
2	13.0	12.5
4	11.5	12.1
6	8.8	10.0
8	6.0	9.2
10	4.2	8.3
12	3.0	6.2
% of Improvement	80.3%	54.07%

In this study, the overall improvement after 12 weeks of treatment with topical adapalene was 80.30% and with topical tazarotene it was 54.07%.

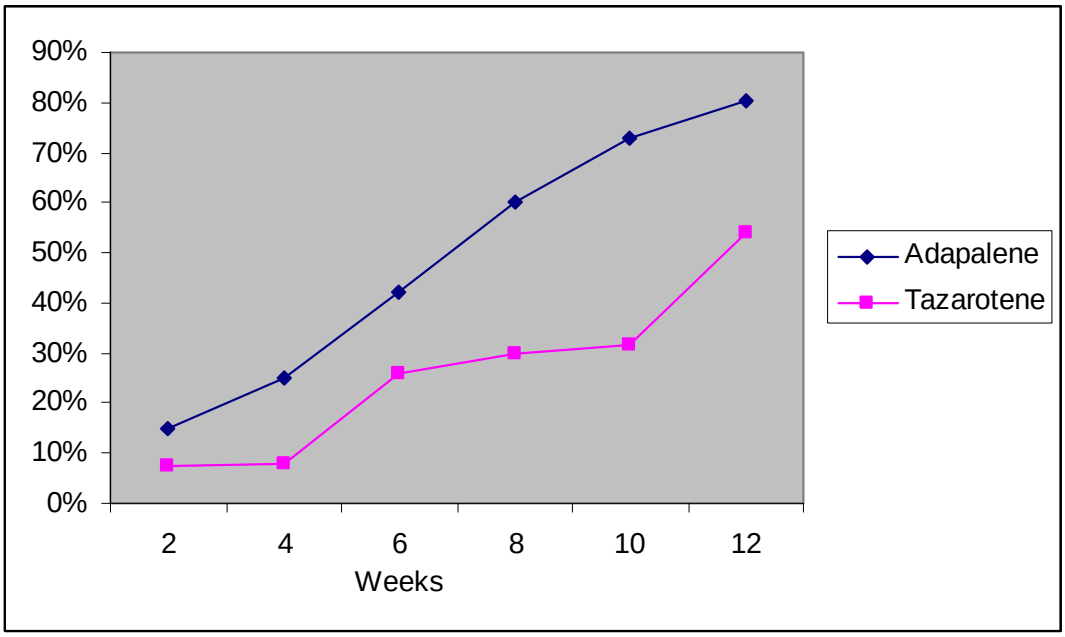
Comparison of Percentage of reduction of acne lesions after every 2 weeks

Weeks	Group – I	Group – II
2	15	7.4
4	25	7.7
6	42	25.9
8	60	29.8
10	73	31.8
12	80.3	54.07

COMPARISON OF PERCENTAGE REDUCTION OF ACNE LESIONS AFTER EVERY 2 WEEKS



COMPARISON OF REDUCTION OF ACNE LESIONS AFTER EVERY 2 WEEKS IN PERCENTAGE



Treatment
with
0.1% Adapalene Cream

BEFORE TREATMENT

12 WEEKS AFTER TREATMENT

BEFORE TREATMENT

12 WEEKS AFTER TREATMENT

BEFORE TREATMENT

12 WEEKS AFTER TREATMENT

BEFORE TREATMENT

12 WEEKS AFTER TREATMENT

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12 WEEKS AFTER TREATMENT

BEFORE TREATMENT

12 WEEKS AFTER TREATMENT

BEFORE TREATMENT

12 WEEKS AFTER TREATMENT

BEFORE TREATMENT

1 WEEK AFTER ADAPALENE TREATMENT

BEFORE TREATMENT

12 WEEKS AFTER TREATMENT

Treatment
with
0.1% Tazarotene Cream

BEFORE TREATMENT

12 WEEKS AFTER TREATMENT

BEFORE TREATMENT

12 WEEKS AFTER TREATMENT

BEFORE TREATMENT

12 WEEKS AFTER TREATMENT

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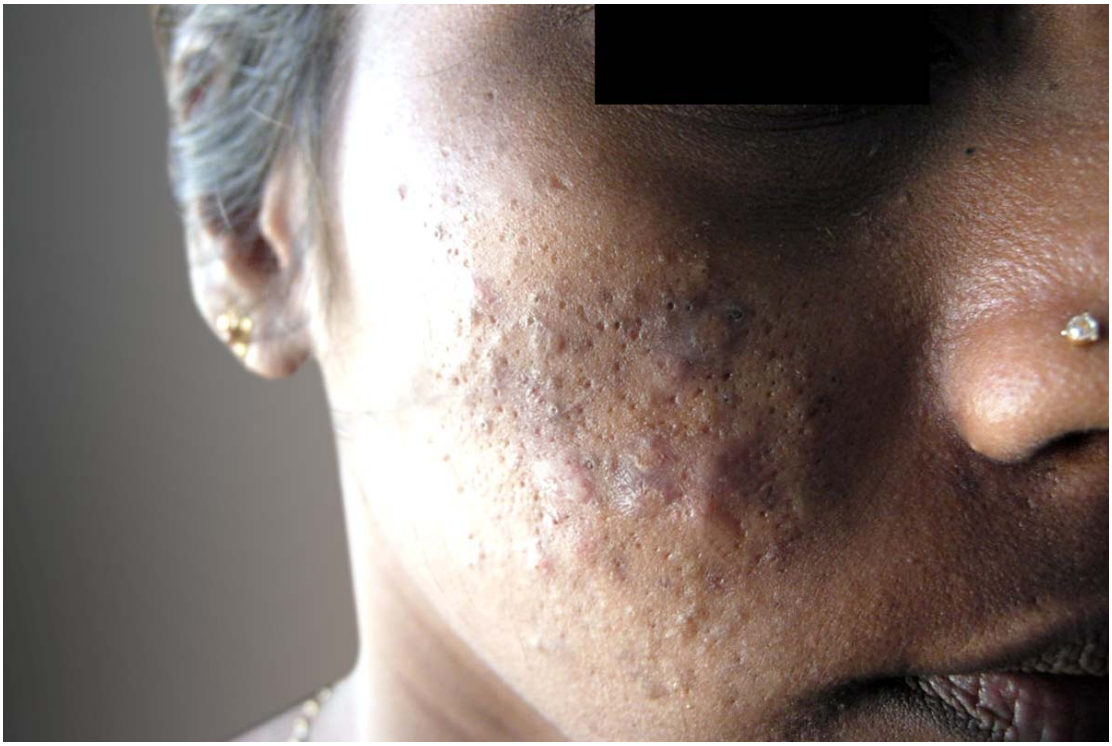
BEFORE TREATMENT

12 WEEKS AFTER TREATMENT



BEFORE TREATMENT

12 WEEKS AFTER TREATMENT

BEFORE TREATMENT

1 WEEK AFTER THERAPY

BEFORE TREATMENT

1 WEEK AFTER TREATMENT

BEFORE TREATMENT

1 WEEK AFTER TREATMENT

DISCUSSION

Acne vulgaris, the “Stigma of Adolescence” exceeds all other causes of suffering in adolescence age group. Many patients do not seek physician’s advice. Many cosmetically conscious adolescents who are to be married shortly came for treatment, however mild the condition may be. In this study, the increased prevalence of acne among students signifies its direct correlation with increased sebaceous activity.

Family history of acne vulgaris was present in 31% of patients. Hereditary factor in the causation of acne has been documented.

15% female patients reported pre-menstrual flare up, this is said to be due to pre-menstrual change in the hydration of pilosebaceous epithelium. Exacerbation of acne lesion during the time of physical and mental stress and summer exacerbation have all been observed.

Acne therapy aims at reduction of sebum production, correcting the abnormal ductal keratinisation, reducing the colony of propionibacterium acnes and preventing the release of inflammatory mediators that are basically responsible for the pathogenesis of acne.

GROUP – I

Patients in this group showed a moderate to good response and there was greater reduction of inflammatory and non inflammatory acne lesions. At the end of 4 weeks, there was 25% reduction of acne lesions and at the end of 8 weeks, the reduction rate was 60%. At the end of 12 weeks of treatment, there was moderate to good response, and the reduction at that time was 80.3%.

The side effects such as irritation, itching, dryness, erythema, skin peeling were seen among few patients. There side effects were very minimal and transient compared to topical 0.1 % tazarotene cream. During treatement with topical 0.1% adaplene cream patient compliance and overall outcomes were good. Patients showed up for regular and proper treatment. The side effects were observed among few patients only, most of the patients had no side effects .

GROUP – II

Patients in this group showed a mild response in both inflammatory and non inflammatory lesions. The side effects were very severe in this study. Most of the patients developed erythema, scaling,

dryness during the Ist week of therapy. The side effects observed in this group were prolonged and severe compared to topical adapalene.

At the end of 4 weeks of treatment, the reduction rate was 7%.

At the end of 12 weeks, the overall reduction was 50.04%

The side effects which have been seen in this study has also been noted in the literature.[54, 55]

Overall, there is moderate to good improvement in the acne lesions with topical 0.1% adapalene cream. Topical treatment with 0.1% tazarotene showed mild improvement with more side effects.

The overall improvement with topical 0.1% tazarotene which were found in the literature were not noted in this study. [54, 55, 57]

According to previous studies conducted at various institutes and research centres [56,57] , the side effects observed with topical adaplene cream were significantly lower than that of topical tazarotene cream as observed in this study. [56, 57, 58]

According to previous studies tazarotene was associated with a significantly greater incidence of patients achieving 50% or greater improvement compared with adapalene. But in this study adapalene was associated with a significantly greater incidence of patients achieving greater improvement. (80% vs. 50% P = 0.01). compared with tazarotene.[56, 58, 59, 60]

CONCLUSION

- In this study, Acne Vulgaris showed increased prevalence among males.
- The increased prevalence was noted in the age group of 15-20 years irrespective of the sex.
- In this study, pronounced incidence of acne vulgaris was noted among students.
- The precipitating factors noted in this study were more among male patients.
- Patients treated with 0.1% adapalene cream showed better response compared to patients treated with 0.1% tazarotone cream.
- Among those improved with topical adapalene cream and topical tazarotene cream good response was observed in the age group of 15-20 years.

- Nearly 75% of the lesions resolved after 10 weeks of treatment with topical adapalene, where as only 30% of the lesions resolved with topical tazarotene.

- The side effects of topical adapalene cream were very minimal and transient the side effects with topical tazarotene were severe and prolonged.

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PROFORMA

Name : Date:

Age : S.No.

Sex : O.P. No.

Occupation

Address

Marital Status

Present Complaints

Duration

H/o Previous topical or Systemic treatment for acne

H/o Drug Intake

H/o precipitating factors such as

Sun Exposure

Premenstrual Flare

Stress

Smoking

Past History

H/o topical / systemic treatment for acne

H/o any other drugs intake

Family History

Personal History

Menstrual History

General Examinations

Systemic Examinations

Dermatological Examination

Distribution

Grading

Associated Dermatoses

Follow Up

Weeks

Lesions	0	2	4	6	8	10	12
Comedones							
Papules							
Pustules							
Total Lesions							

Side Effects

	1	2	4	6	8	10	12
Burning							
Erythema							
Peeling							
Exacerbation							
Itching							
Infection							
Other							

Response

Nil	Mild	Moderate	Good

MASTER CHART

S.NO.	AGE	SEX	OCC	DUR	PPF	PT	TR	RESPONSE - WKS			% RED.	S.E	OD
								0	8	12			
1	15	M	S	6 m	sum, st	T	A	8	5	Nil	100	E	
2	15	F	S	1 y	st		A	12	4	3	75	I	
3	17	M	S	1 y	st		A	15	4	2	86	EX	
4	16	M	S	2 y	sum, st		A	8	2	0	100	EX	
5	16	M	S	1 y	st		A	13	4	3	76		PV
6	16	M	S	1 y	st	T	A	14	10	5	64	B	
7	17	F	S	1 y	sum		A	12	2	1	91		PLE
8	17	F	S	2 y	st		A	14	10	4	71	E	SD
9	17	F	S	1 y	sum, st	T	A	12	8	5	58		
10	17	M	S	2 y	st		A	12	4	3	66	D	SD
11	18	M	S	2 y		T	T	9	6	5	44	B	
12	20	M	S	3 y			T	12	9	6	50	E	SD
13	19	M	S	1 y	smo, st		T	9	6	5	44	B	SD
14	20	M	S	2 y		T	T	8	5	4	50	E, D	
15	20	M	S	3 y	smo, st		T	8	5	4	50	D, I	SD
16	22	M	S	3 y	smo		T	9	7	4	55	E, I	
17	18	M	S	2 y			T	6	3	2	66		
18	19	F	S	2 y	sum	T	T	8	5	4	50	B, D	PLE
19	19	F	S	2 y	sum		T	8	4	4	50		SD
20	18	M	S	1 y			T	8	4	2	75		
21	17	M	S	1 y	st	T	A	9	6	3	77		
22	16	M	S	2 y			A	5	3	1	80		
23	19	M	S	11m			A	9	6	3	66		
24	20	M	S	2 y			A	10	5	2	80	B, D	
25	19	M	S	3 y			A	7	4	1	85		
26	20	M	S	2 y	smo		A	8	5	2	75	B	
27	19	M	S	3 y			A	8	3	3	62	I	
28	19	M	S	2 y			A	9	5	3	77	B	PV
29	18	M	S	2 y			A	5	3	1	80		
30	17	M	S	1 y	st		A	9	6	3	66	B	PLE
31	16	M	S	1 y			A	10	5	2	80		
32	17	M	S	2 y	st		A	7	4	1	85	B	
33	18	M	S	2 y	sum, smo	T	A	8	5	2	75	I	
34	20	M	S	1 y	smo		A	8	3	3	62	B	
35	19	M	S	2 y	sum, smo	T	A	9	5	2	77	E	
36	18	M	S	1 y	smo		T	8	3	2	75	P, D	SD
37	18	M	S	3 y	sum	T	T	10	5	1	90	P, D	
38	17	M	S	2 y	smo		T	10	6	3	70	E, B	
39	16	M	S	2 y	st	T	T	6	4	0	100		
40	17	M	S	2 y	sum		T	9	4	2	77	E, B	
41	17	M	S	3 y	st		T	8	4	0	100	I	
42	18	M	S	2 y	sum	T	T	10	5	3	70	E, B	SD
43	17	M	S	1 y	smo		T	7	5	4	42	I	
44	17	F	S	2 y	st		T	8	5	4	50	E, B	

45	18	F	S	2 y	st		T	7	5	4	42	I	
46	19	M	S	2 y			T	10	6	5	50	E, B	
47	17	M	S	1 y	smo, st	T	T	8	5	4	50	P	
48	17	M	S	1 y	st		T	10	6	4	60	E, B	
49	18	M	S	2 y	st		T	8	4	3	62	P	PLE
50	19	M	S	2 y	st	T	T	7	6	2	7	E, B	
51	19	M	S	2 y	smo		T	14	11	9	35	P	
52	21	F	O	2 y		T	T	13	10	8	61	I	PV
53	22	M	O	2 y	smo		T	11	8	5	54	E, B	
54	20	M	S	2 y	sum, smo	T	T	10	8	5	50	D	
55	24	M	UE	2 y	st		T	14	11	7	50	E, B	PLE
56	25	F	UE	3 y	st	S	T	12	8	6	50	D	
57	20	F	O	2 y	st	T	T	15	11	8	46	D	
58	19	M	S	2 y	st		T	14	8	6	57	D	PLE
59	21	M	S	2 y	sum, smo		T	11	5	4	63	D	
60	22	M	O	3 y		T	T	12	8	6	50	D	
61	22	M	O	4 y	sum, smo		T	9	5	4	55	D	
62	24	M	UE	5 y	smo	T	T	18	12	9	50	D	
63	25	M	O	5 y	smo		T	16	11	9	43	D	
64	24	M	O	5 y	smo	T	T	10	7	5	50	D	
65	23	M	O	4 y	smo		T	14	8	5	64	D	
66	23	M	O	5 y		T	T	11	7	4	63		
67	19	F	S	4 y	st		T	15	10	9	40		PV
68	18	F	S	3 y	st	T	T	10	6	5	70		PV
69	19	F	S	4 y	st	T	T	10	6	4	60		SE
70	20	F	S	4 y	pm, sum		T	14	10	7	50		D
71	19	F	S	3 y	st		T	12	8	6	50		D
72	20	F	S	2 y	pm, sum	T	T	16	11	7	56		D
73	19	F	S	1 y	st	S	T	14	9	5	64		I
74	19	F	UE	1 y	pm		T	13	10	6	53		D
75	19	M	UE	1 y	sum, smo	T	T	12	9	6	50		D
76	24	M	S	2 y	smo		A	14	9	3	78		
77	26	M	S	6 y	sum		A	10	6	0	100		
78	26	F	O	8 y	pm	T	A	14	7	2	85		E
79	21	F	O	3 y	pm		A	13	7	3	76		
80	22	F	S	3 y	pm	S	A	10	4	3	70		E, B
81	22	F	HW	4 y	st		A	10	6	4	60		
82	22	F	S	5 y	pm	S	A	8	3	3	62		E
83	23	F	S	5 y	st		A	10	8	4	60		I
84	20	F	S	4 y	pm	S	A	9	4	1	88		E, B
85	21	F	O	4 y	sum		A	10	6	2	60		
86	22	F	HW	5 y	pm	S	A	10	4	4	50		E
87	23	F	S	5 y	sum		A	9	5	1	85		D
88	24	F	O	5 y	st	T	A	10	7	4	60		
89	20	F	S	4 y	pm		A	10	7	4	60		E, B
90	25	F	O	3 y	pm	S	A	8	5	0	100		
91	23	F	O	4 y		T	A	9	3	2	77		E
92	22	F	S	5 y			A	8	5	1	87		EX

93	26	F	O	8 y		T	A	8	4	1	87		EX
94	26	M	UE	7 y	smo		A	7	5	0	100		
95	20	M	UE	2 y	smo	T	A	7	3	1	85		I
96	29	M	O	1 y	smo		A	11	4	1	90		EX
97	26	M	UE	2 y	sum, smo	S	A	8	5	0	100		I
98	23	M	S	2 y	smo		A	7	5	1	85		
99	24	M		5 y	sum, smo	S	A	7	3	0	100		EX
100	23	M		3 y	sum, smo	S	A	9	3	2	77		I

A	:	ADAPALENE											
B	:	BURNING											
D	:	DRYNESS											
DUR	:	DURATION											
E	:	ERYTHEMA											
Ex	:	EXACERBATION											
HW	:	HOUSE WIFE											
I	:	ITCHING											
M	:	MONTH											
OD	:	OTHER DISEASES											
P	:	PREMENSTRUAL FLARE											
PPF	:	PRECIPITATING FACTOR											
PT	:	PREVIOUS TREATMENT											
PLE	:	POLYMORPHIC LIGHT ERUPTION											
S	:	STUDENT											
Sum	:	SUMMER EXACERBATION											
Smo	:	SMOKING											
ST	:	STRESS											

SD	:	SEBORRHOEIC DERMATITIS											
RED	:	REDUCTION											
TR	:	TREATMENT											
UE	:	UNEMPLOYED											
O	:	OTHERS OCCUPATION											
OD	:	OTHER DISEASES											
Y	:	YEAR											